WHAT IS CLAIMED IS:

1   1. A humanized immunoglobulin comprising a humanized
2   heavy chain and a humanized light chain:
3   (1) the humanized light chain comprising three
4   complementarity determining regions (CDR1, CDR2 and CDR3)
5   having amino acid sequences from the corresponding
6   complementarity determining regions of a mouse 21-6
7   immunoglobulin light chain, and a variable region framework
8   from a human kappa light chain variable region framework
9   sequence except in at least one position selected from a first
10 group consisting of L45, L49, L58 and L69, wherein the amino
11 acid position is occupied by the same amino acid present in the
12 equivalent position of the mouse 21-6 immunoglobulin light
13 chain variable region framework; and
14   (2) the humanized heavy chain comprising three
15 complementarity determining regions (CDR1, CDR2 and CDR3)
16 having amino acid sequences from the corresponding
17 complementarity determining regions of a mouse 21-6
18 immunoglobulin heavy chain, and a variable region framework
19 from a human heavy chain variable region framework sequence
20 except in at least one position selected from a group
21 consisting of H27, H28, H29, H30, H44, H71, wherein the amino
22 acid position is occupied by the same amino acid present in the
23 equivalent position of the mouse 21-6 immunoglobulin heavy
24 chain variable region framework;
25   wherein the immunoglobulin specifically binds to a
26 VLA-4 ligand with a binding affinity having a lower limit of
27 about 10^7 M^{-1} and an upper limit of about five-times the
28 binding affinity of the mouse 21-6 immunoglobulin.

1   2. The humanized immunoglobulin of claim 1 wherein
2   the humanized light chain variable region framework is from an
3   RE1 variable region framework sequence except in at least one
4   position selected from the first group, and except in at least
5   one position selected from a third group consisting of
6   positions L104, L105 and L107, wherein the amino acid position
7   is occupied by the same amino acid present in the equivalent

8   position of a kappa light chain from a human immunoglobulin

9   other than RE1.

1   3.   The humanized immunoglobulin of claim 2, wherein

2   the humanized heavy chain variable region framework is from a

3   21/28'CL variable region framework sequence.

1   4.   The humanized immunoglobulin of claim 3, wherein

2   the humanized light chain variable region framework comprises

3   at least three amino acids from the mouse 21.6 immunoglobulin

4   at positions in the first group and three amino acids from the

5   kappa light chain from the human immunoglobulin other than REI

6   at positions in the third group, and the humanized heavy chain

7   variable region framework comprises at least five amino acids

8   from the mouse 21.6 immunoglobulin at positions in the second

9   group.

1   5.   The humanized immunoglobulin of claim 4, wherein

2   the humanized light chain variable region framework is

3   identical to the RE1 light chain variable region framework

4   sequence except for the at least three positions from the first

5   group and the three positions from the third group, and the

6   heavy chain variable region framework is identical to the

7   21/28'CL heavy chain variable region framework sequence except

8   for the at least five positions from the second group.

1   6.   The humanized immunoglobulin of claim 5, wherein

2   the at least three positions from the first group are positions

3   L45, L58 and L69, and at the least five positions from the

4   second group are positions H27, H28, H29, H30 and H71.

1   7.   The humanized immunoglobulin of claim 6, wherein

2   the humanized light chain comprises complementarity determining

3   regions that are identical to the corresponding complementarity

4   determining regions of the mouse 21-6 heavy chain, and the

5   humanized heavy chain comprises complementarity determining

6   regions that are identical to the corresponding complementarity

7   determining regions of the mouse 21-6 heavy chain, except that

8   the CDR3 region of the humanized heavy chain may or may not
9   comprise a phenylalanine residue at position H98.

1   8.   The humanized immunoglobulin of claim 7, wherein
2   the CDR3 of the humanized heavy chain comprises a phenylalanine
3   residue at position H98.

1   9.   The humanized immunoglobulin of claim 1, wherein
2   the amino acid sequence of the mature light chain variable
3   region is the sequence designated La (SEQ ID NO: 7) in Fig. 6.

1   10. The humanized immunoglobulin of claim 1, wherein
2   the amino acid sequence of the mature light chain variable
3   region is the sequence designated Lb (SEQ ID NO: 8) in Fig. 6.

1   11. The humanized immunoglobulin of claim 1, wherein
2   the amino acid sequence of the mature heavy chain variable
3   region is the sequence designated Ha (SEQ ID NO: 11) in Fig. 7.

1   12. The humanized immunoglobulin of claim 1, wherein
2   the amino acid sequence of the mature heavy chain variable
3   region is the sequence designated Hb (SEQ ID NO: 12) in Fig. 7.

1   13. The humanized immunoglobulin of claim 1, wherein
2   the amino acid sequence of the mature heavy chain variable
3   region is the sequence designated Hc (SEQ ID NO: 13) in Fig. 7.

1   14. The humanized immunoglobulin of claim 9, wherein
2   the amino acid sequence of the mature heavy chain variable
3   region is Ha (SEQ ID NO: 11) in Fig 7.

1   15. The humanized immunoglobulin of claim 9, wherein
2   the amino acid sequence of the mature heavy chain variable
3   region is Hb (SEQ ID NO: 12) in Fig 7.

1   16. The humanized immunoglobulin of claims 9,
2   wherein the amino acid sequence of the mature heavy chain
3   variable region is designated Hc (SEQ ID NO: 13) in Fig. 7.

1   17. A binding fragment of the humanized
2 immunoglobulin of claim 14 or claim 16.

1   18. A humanized immunoglobulin of claim 14 or 16
2 that has a constant region domain.

1   19. A humanized immunoglobulin of claim 18, wherein
2 the constant region domain has an effector function.

1   20. A humanized immunoglobulin of claim 18 wherein
2 the constant region domain lacks an effector function.

1   21. The humanized immunoglobulin of claim 19,
2 wherein the effector function is capable of complement fixation
3 or antibody dependent cellular toxicity.

1   22. A nucleic acid encoding a heavy chain of a
2 humanized antibody of claim 1 or a binding fragment thereof.

1   23. A nucleic acid encoding a light chain of a
2 humanized antibody of claim 1 or a binding fragment thereof.

1   24. A computer programmed to display a three-
2 dimensional representation of a humanized immunoglobulin of
3 claim 1 on a monitor.

1   25. A pharmaceutical composition comprising a
2 humanized antibody of claim 14 or 16, or a binding fragment
3 thereof, and a pharmaceutically acceptable carrier therefor.

1   26. A method for detecting VLA-4 antigen, the method
2 comprising:
3   administering a humanized immunoglobulin of claim 14
4 or 16, or a binding fragment thereof, to a patient or a tissue
5 sample therefrom; and
6   detecting complexes formed by specific binding
7 between the antibody or fragment and VLA-4 present in the
8 target sample.

1   27. A method of inhibiting adhesion of a leukocyte
2 to an endothelial cell, the method comprising administering a
3 therapeutically effective amount of the pharmaceutical
4 composition of claim 25.

1   28. The method of claim 27, wherein the endothelial
2 cell is a brain cell.

1   29. A method of treating an inflammatory disease in
2 a patient comprising administering to the patient a
3 therapeutically effective amount of the pharmaceutical
4 composition of claim 25.

1   30. The method of claim 29 wherein the inflammatory
2 disease is multiple sclerosis.